



Figure 1

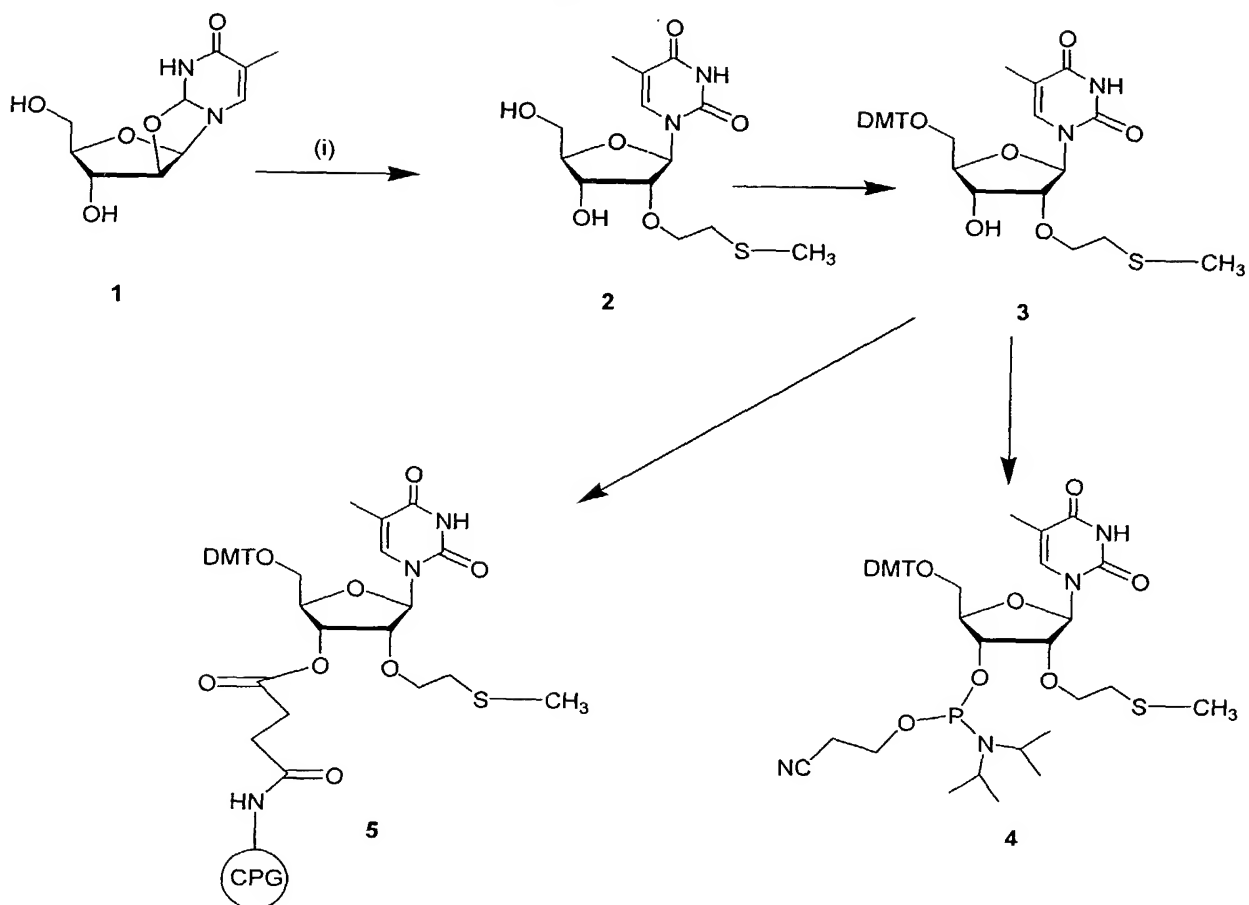
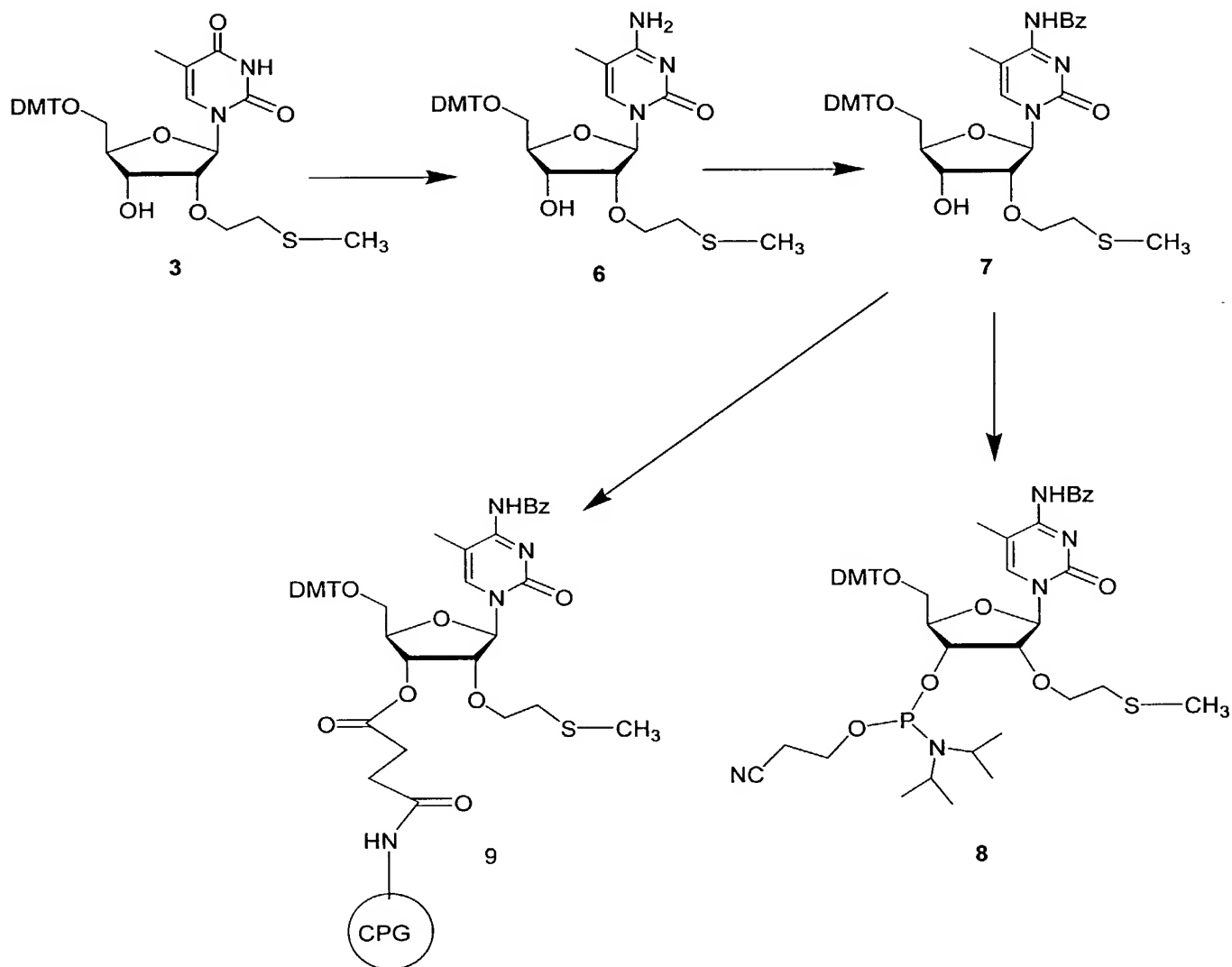




Figure 2





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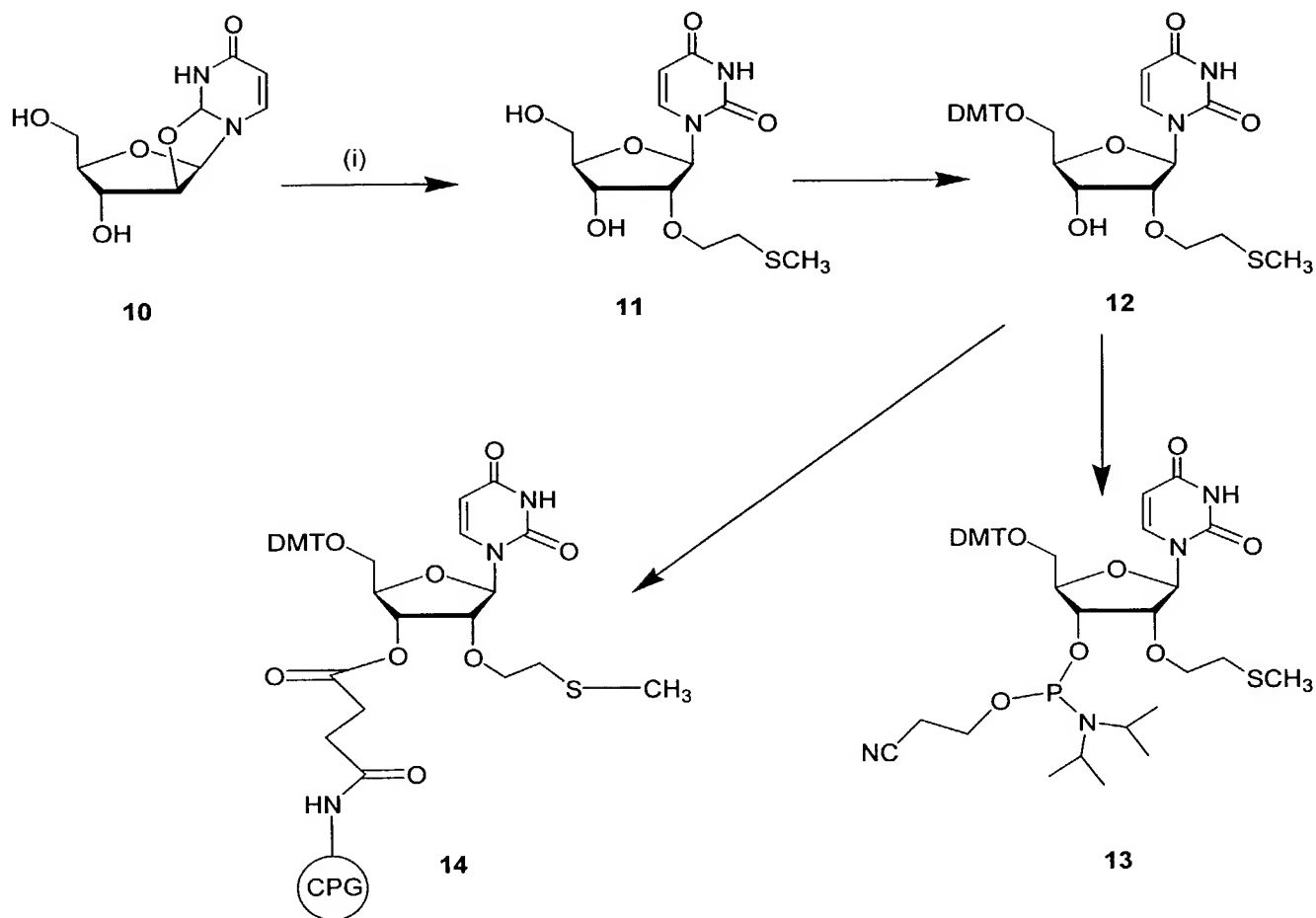
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides

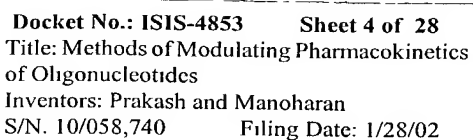
Inventors: Prakash and Manoharan

S/N: 10/058,740

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Figure 3





The reaction scheme illustrates the synthesis of nucleoside phosphoramidites 17 and 18 from nucleoside 12. Nucleoside 12, which contains a 4-oxo-5,6-dihydro-1H-pyrimidin-2-yl group, is first converted to nucleoside 15 by replacing the 4-oxo group with an amino group (NH₂). Nucleoside 15 is then converted to nucleoside 16 by replacing the amino group with a benzoylamino group (NHBz). Nucleoside 16 is then converted to nucleoside 17 by replacing the 4-oxo group with a methylthio group (SCH₃). Finally, nucleoside 17 is converted to nucleoside 18 by replacing the methylthio group with a phosphoramidite group (P(=O)(OCH₂CH₂NC(=O)CPG)OCH₂CH₂NC(=O)CPG).



Figure 5

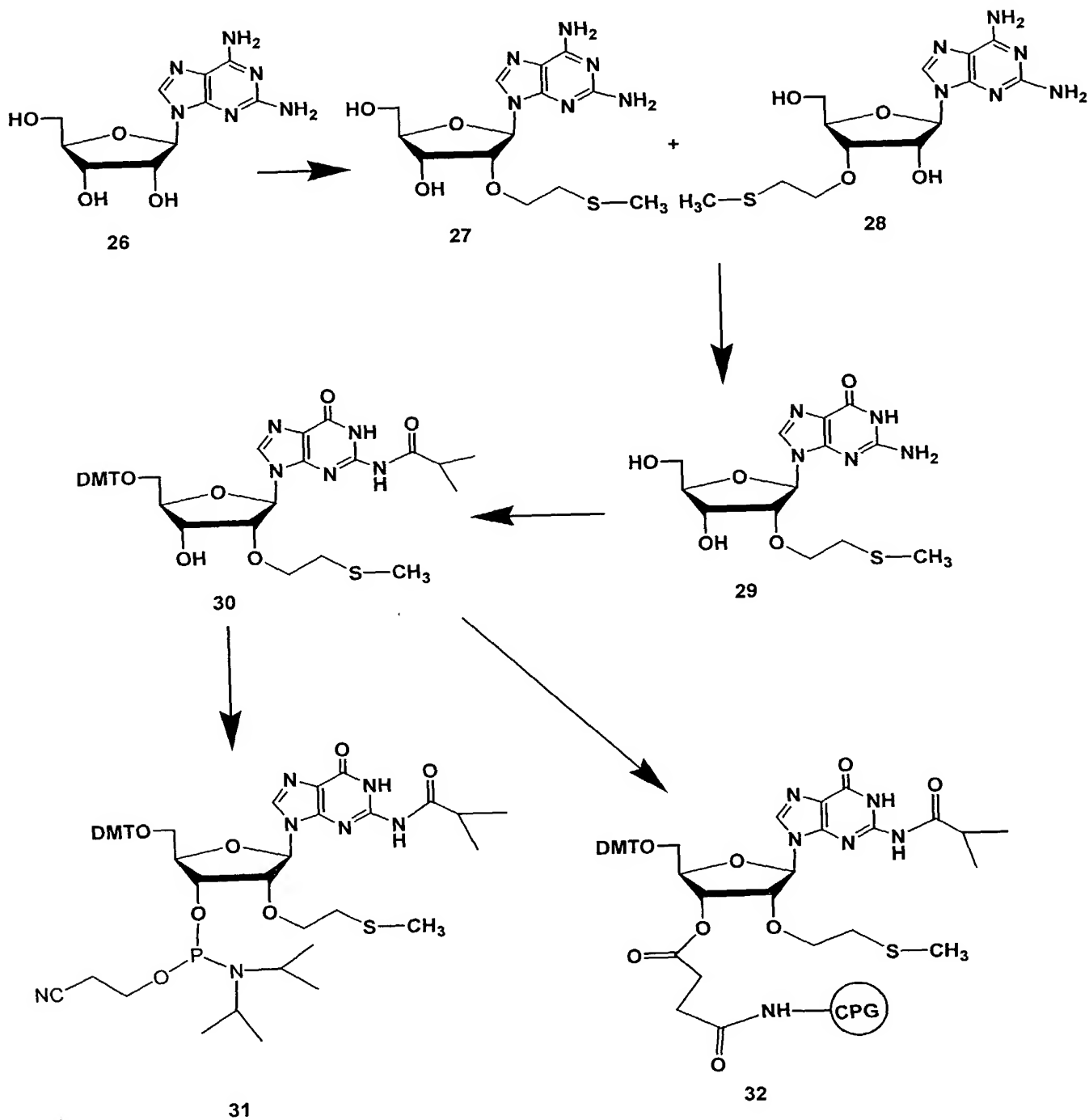




Figure 6

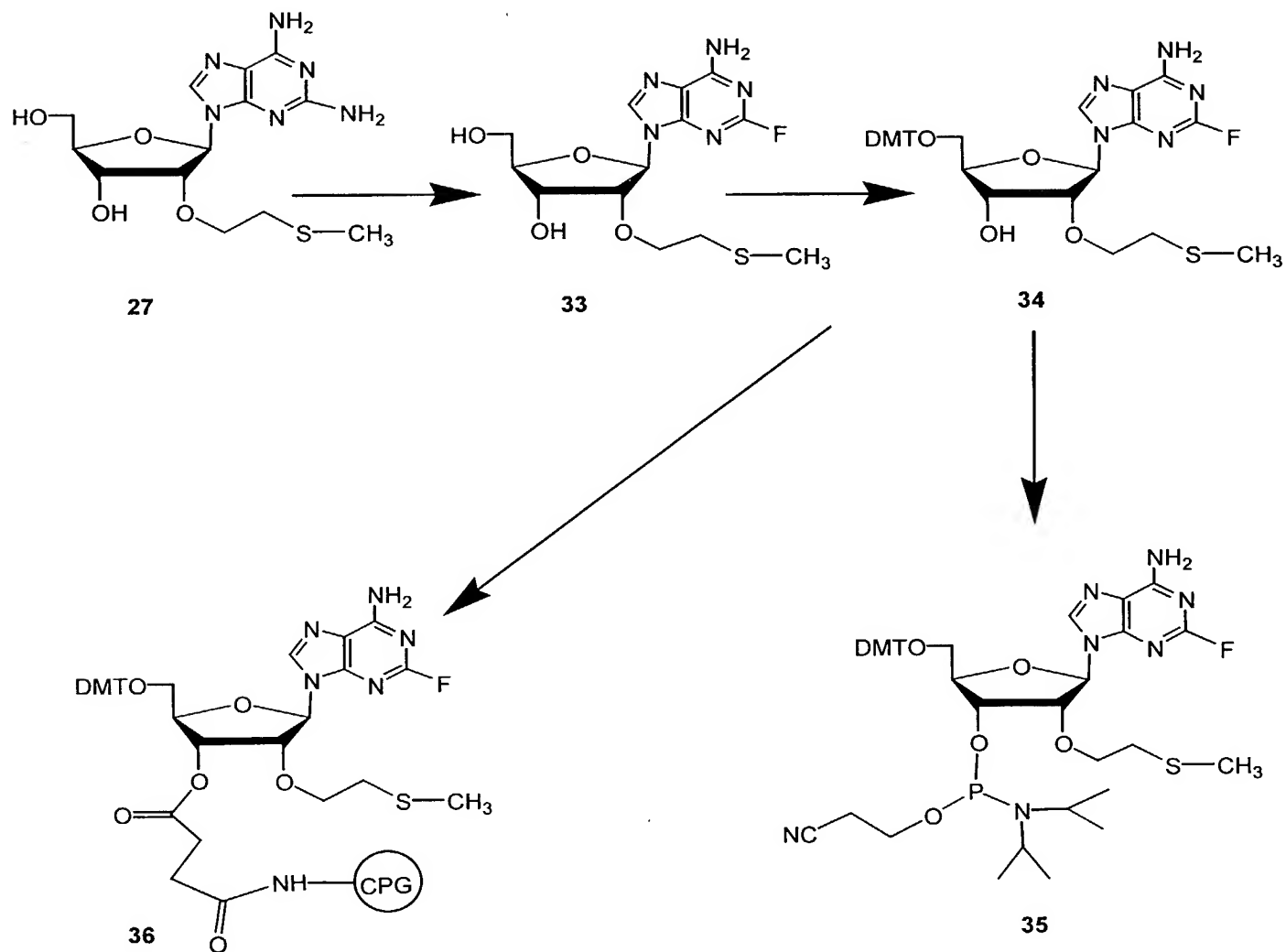




Figure 7

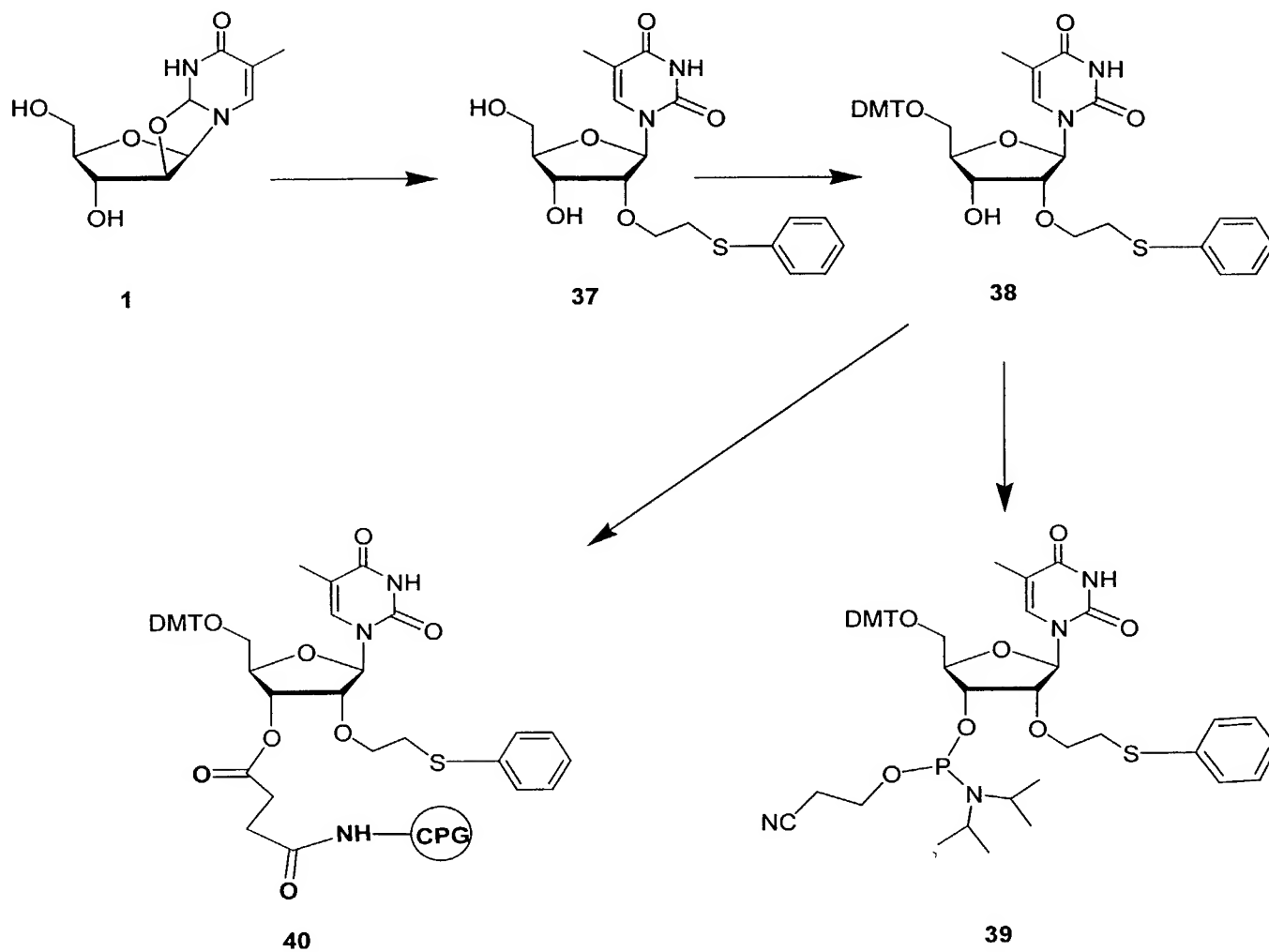




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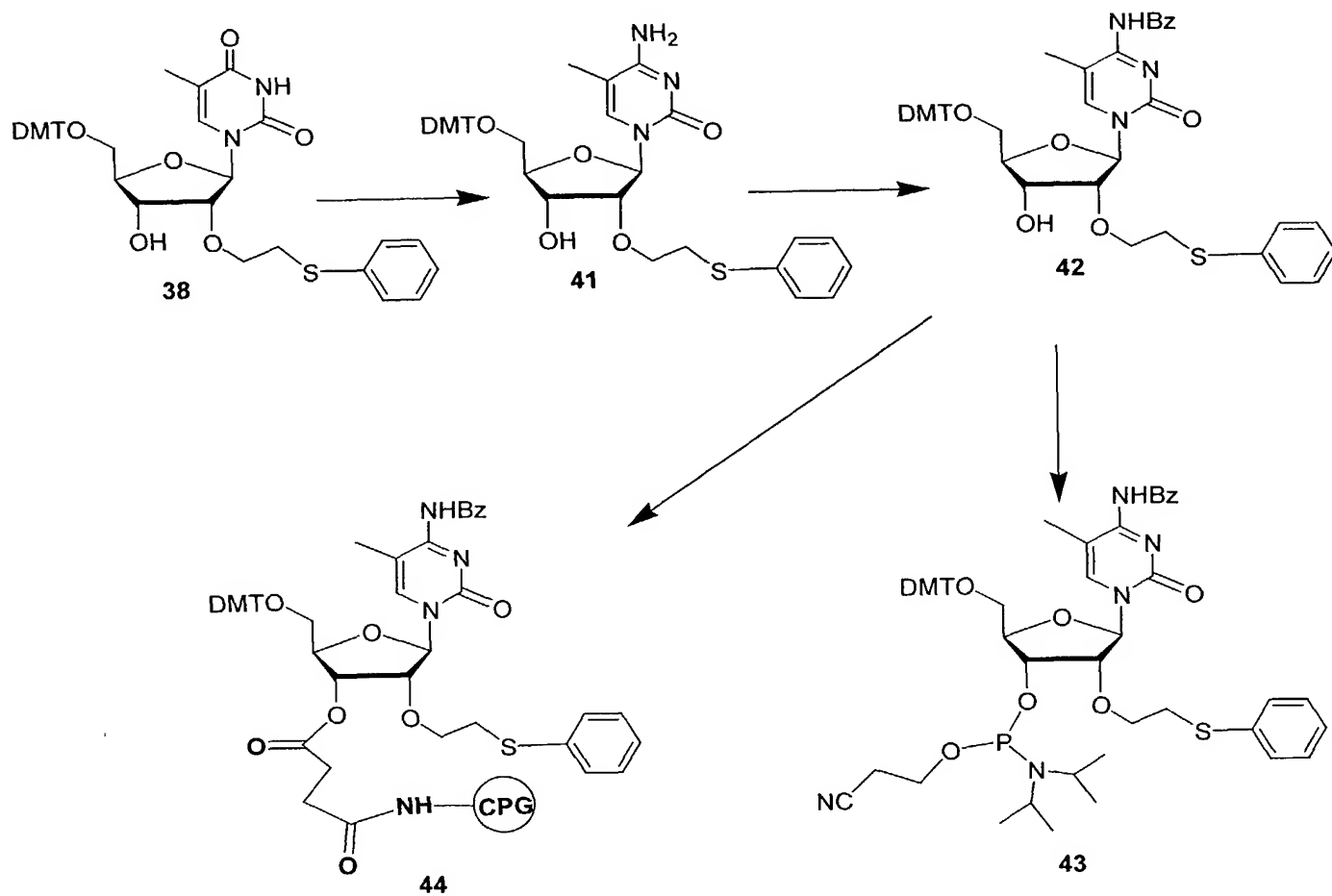




Figure 9

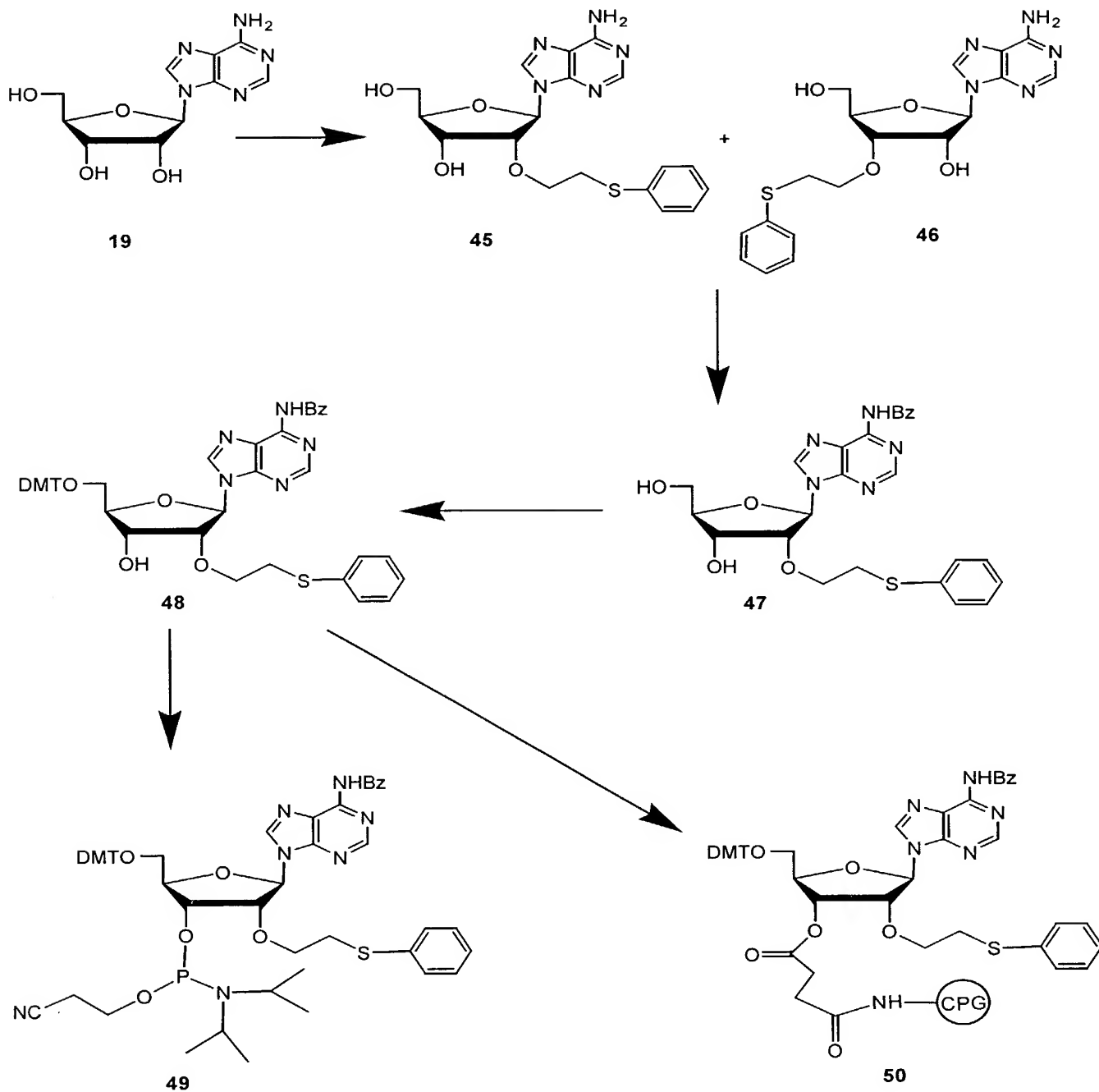




Figure 10

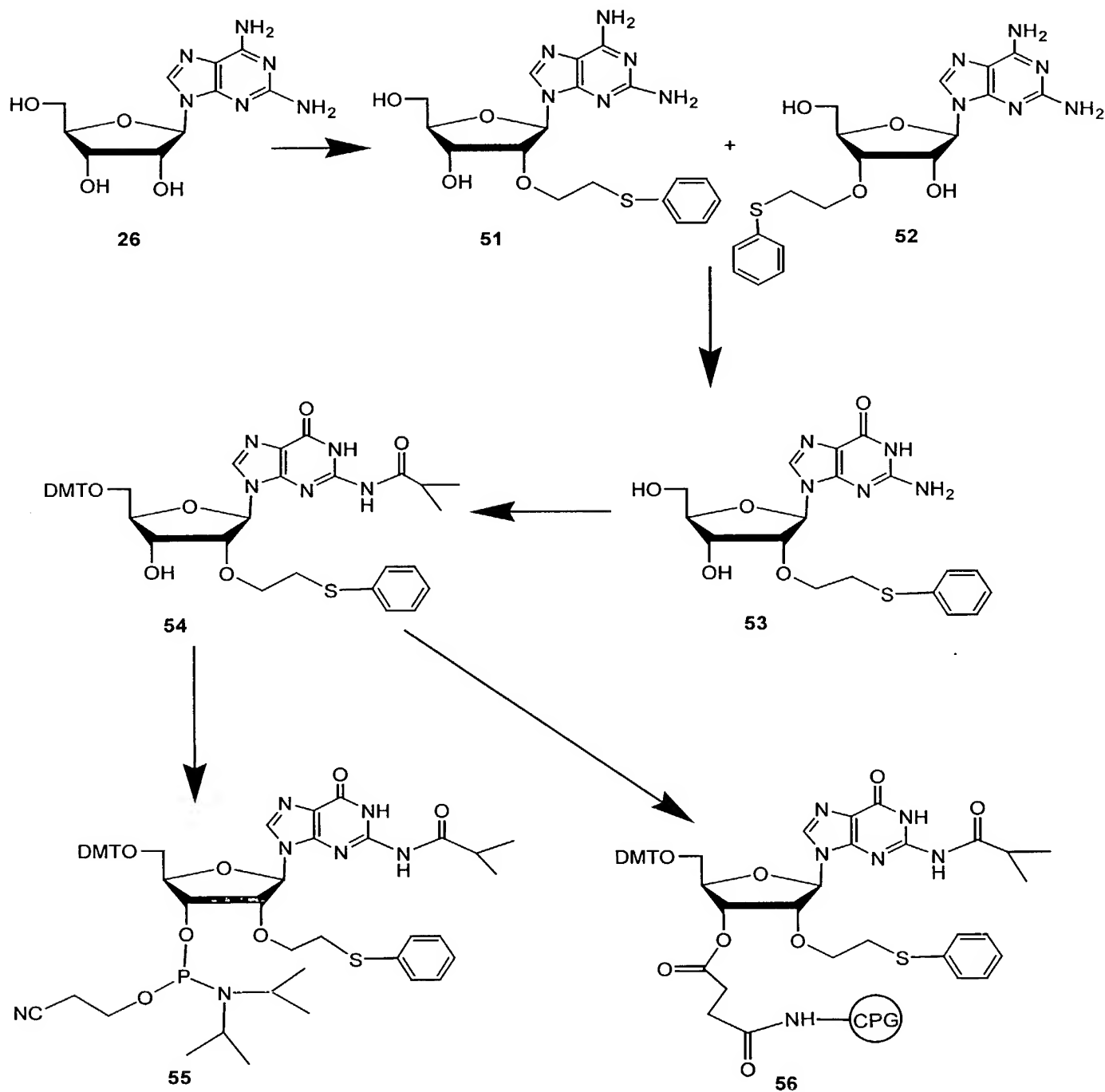
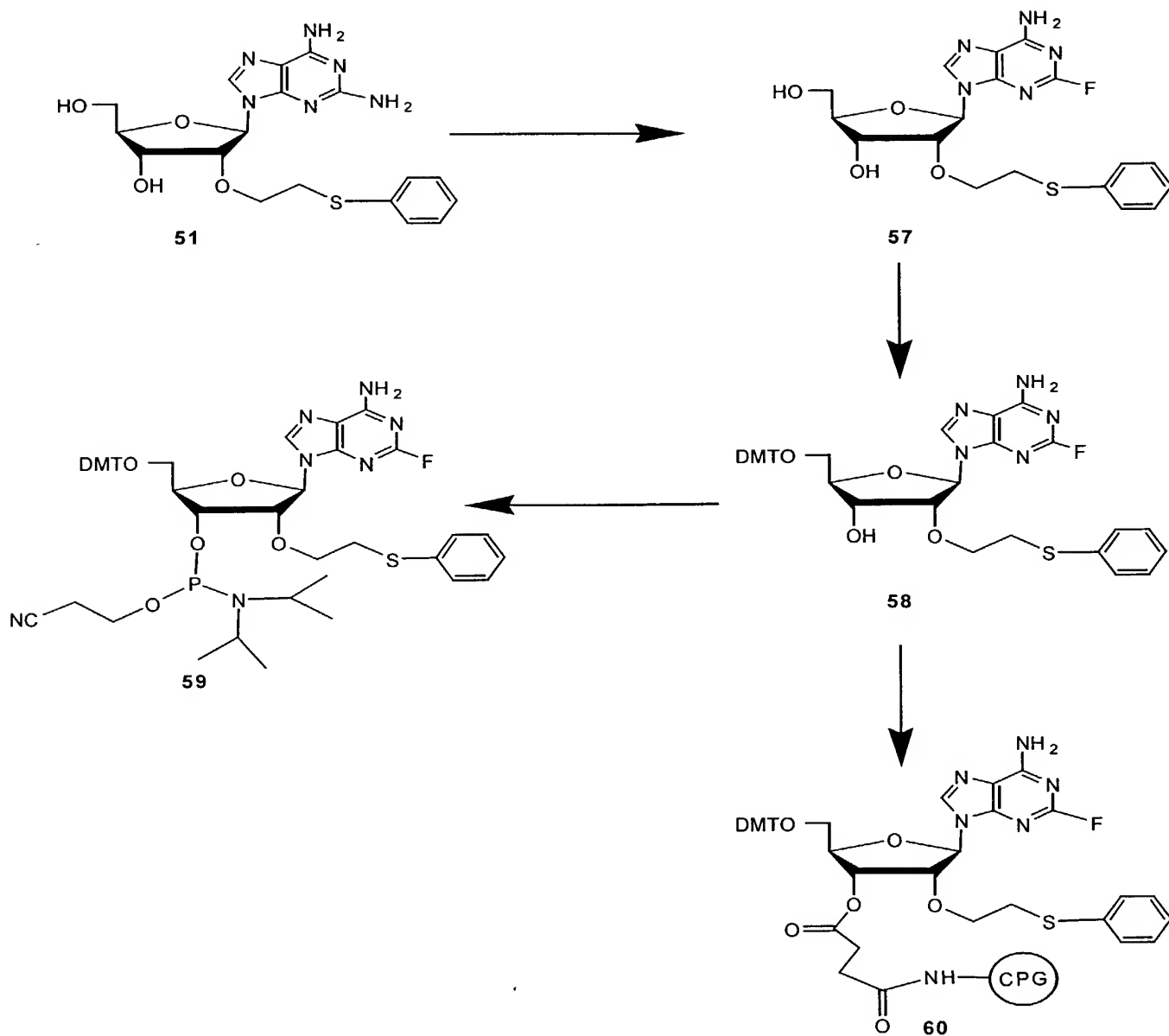




Figure 11





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Figure 12

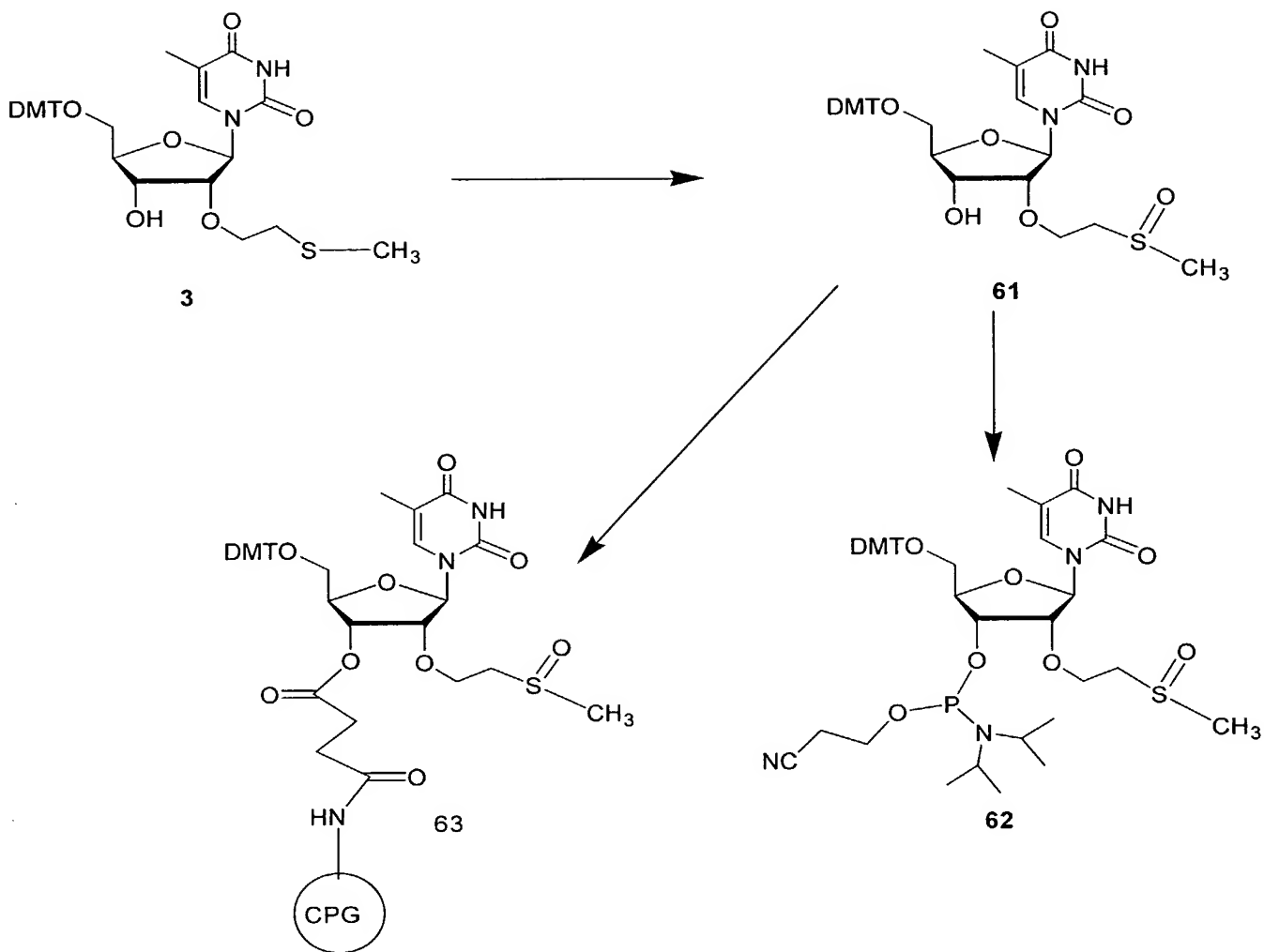
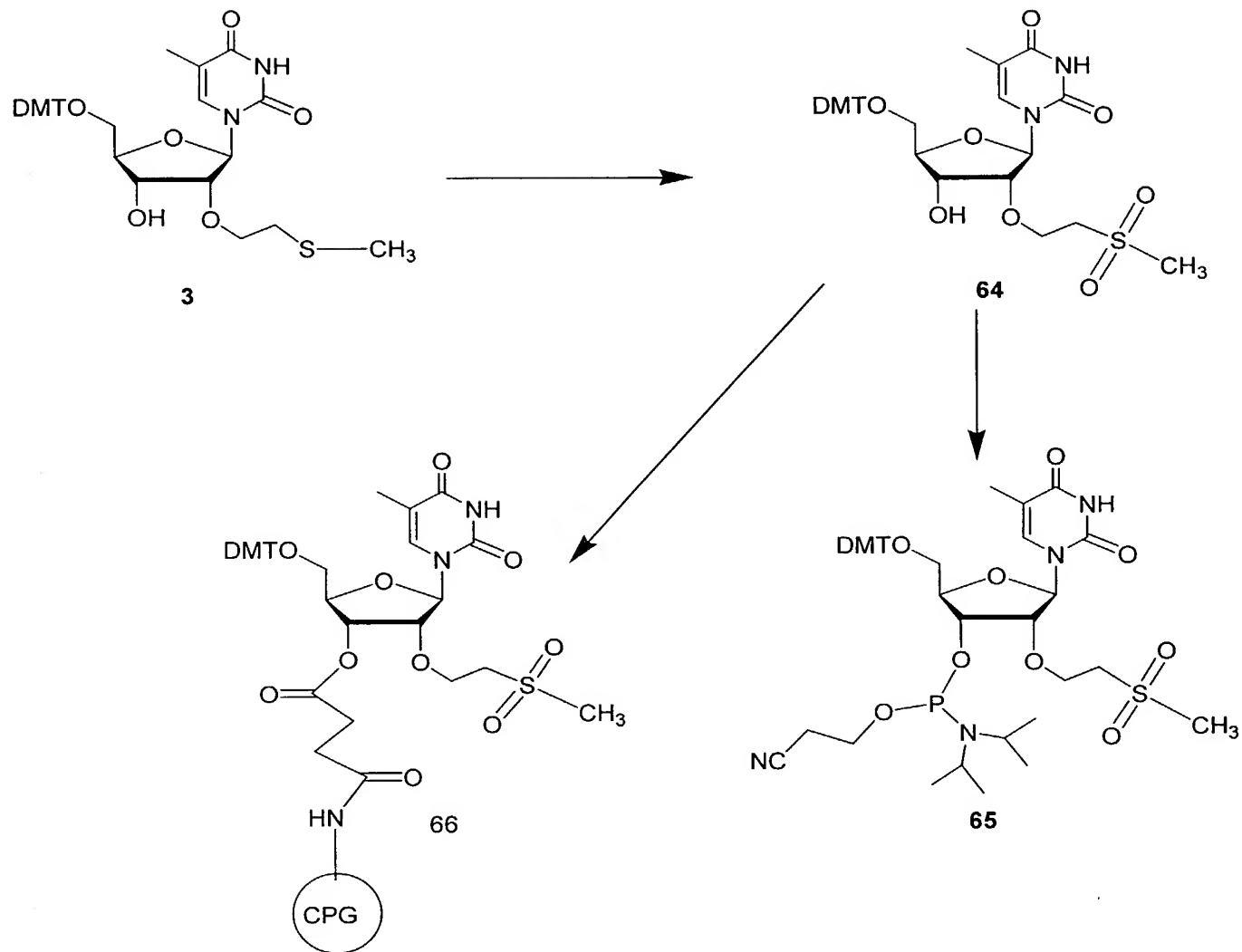




Figure 13

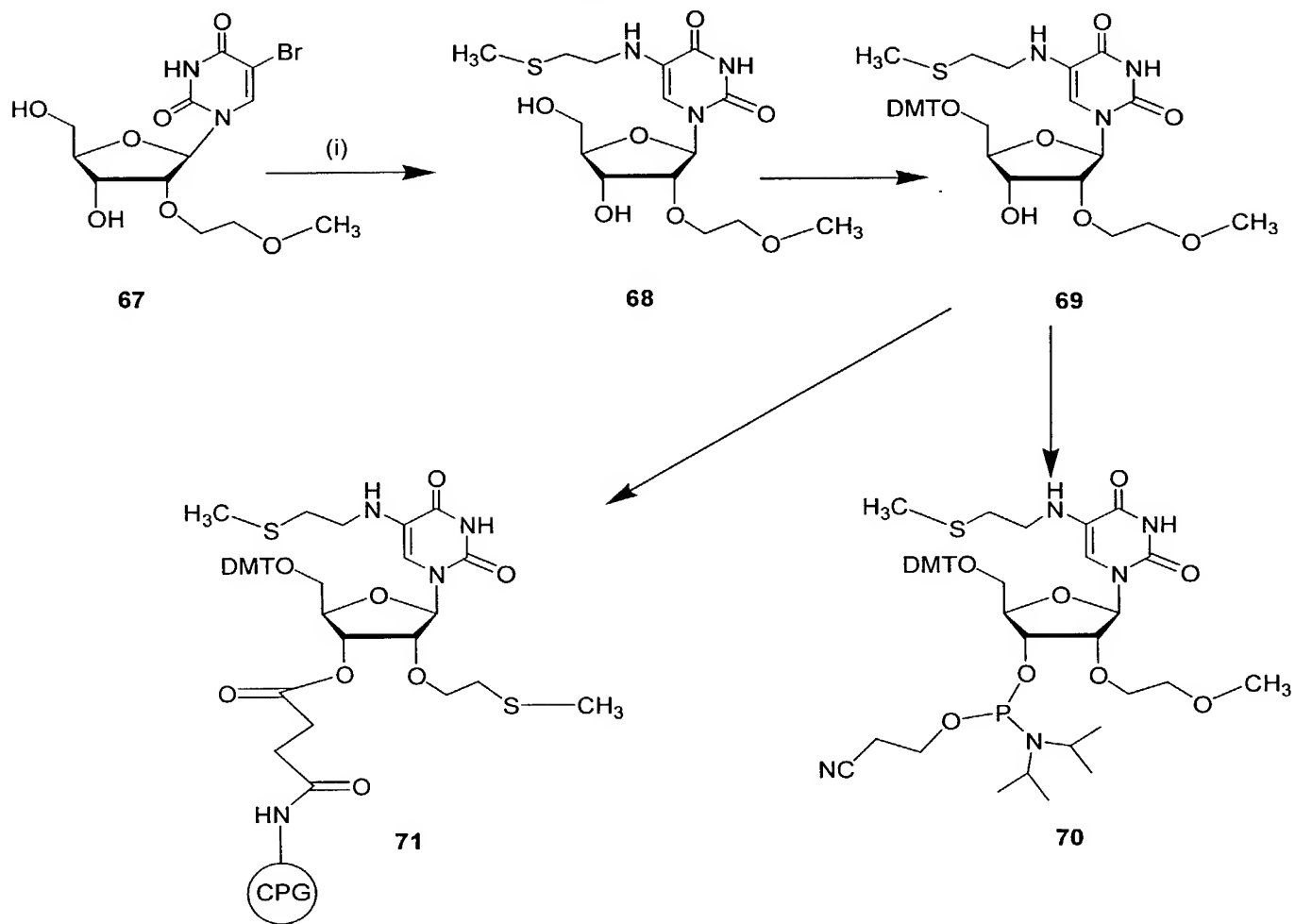




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Figure 14

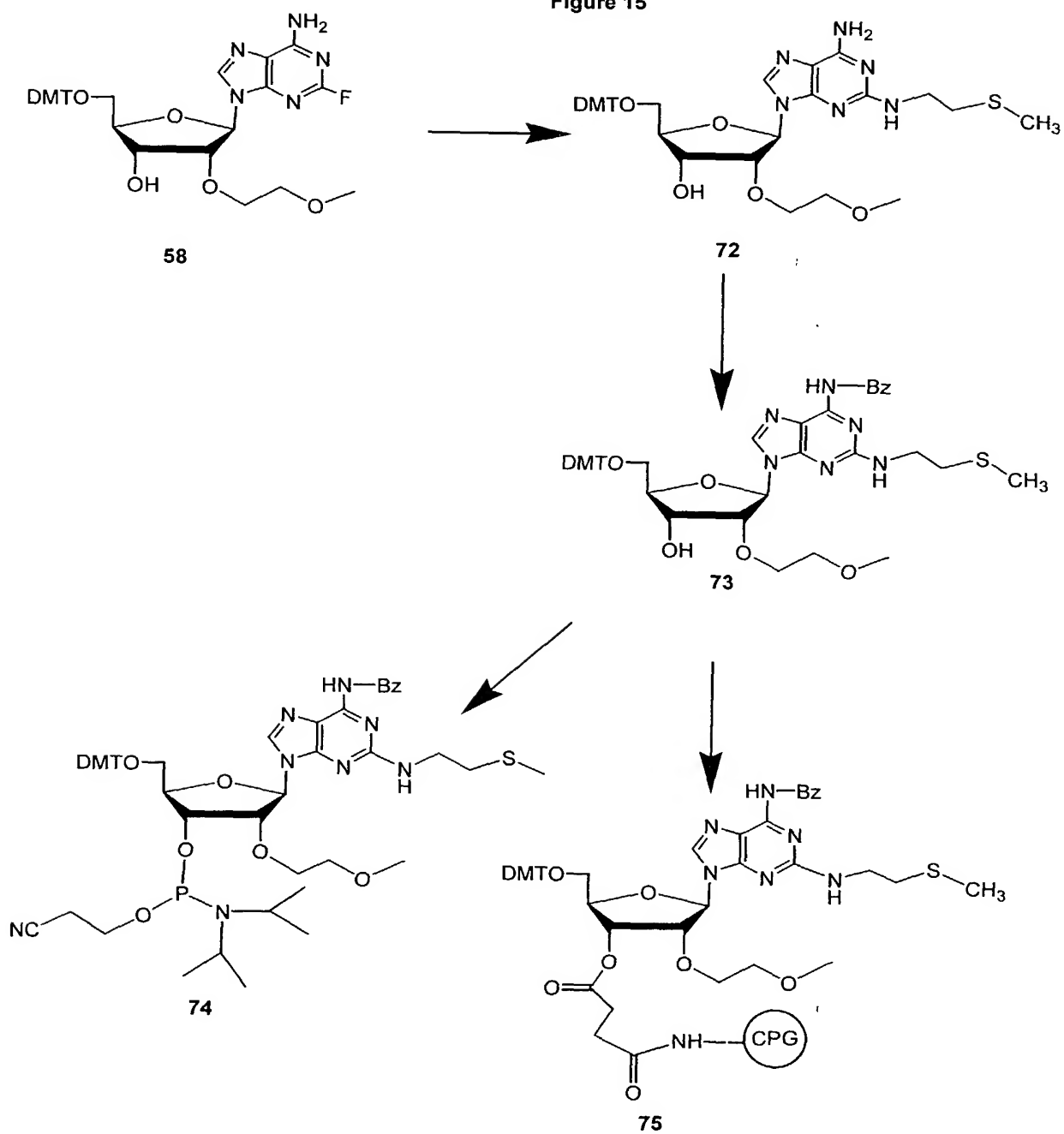




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Figure 15





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of Oligonucleotides
Inventors: Prakash and Manoharan
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Figure 16

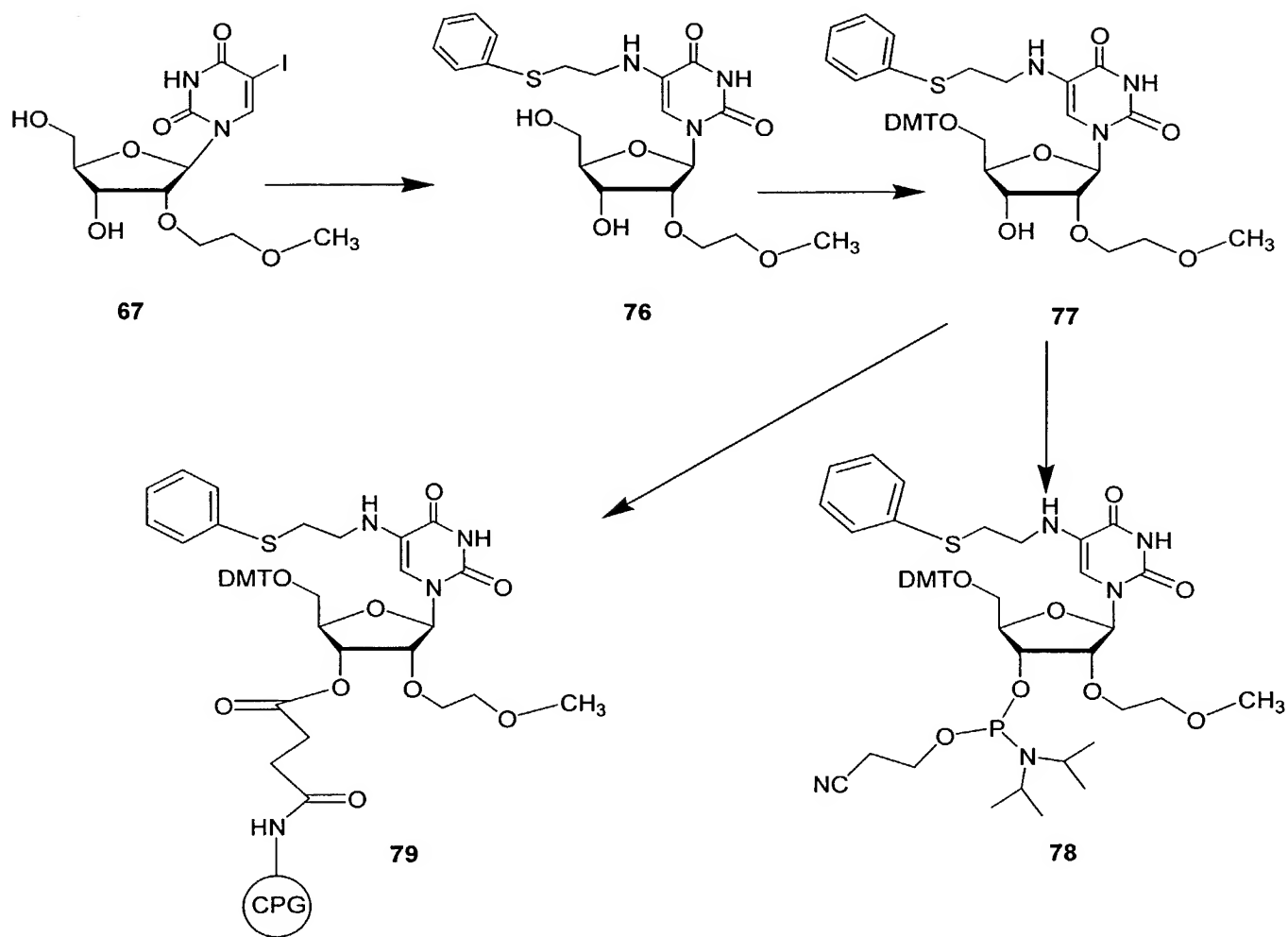
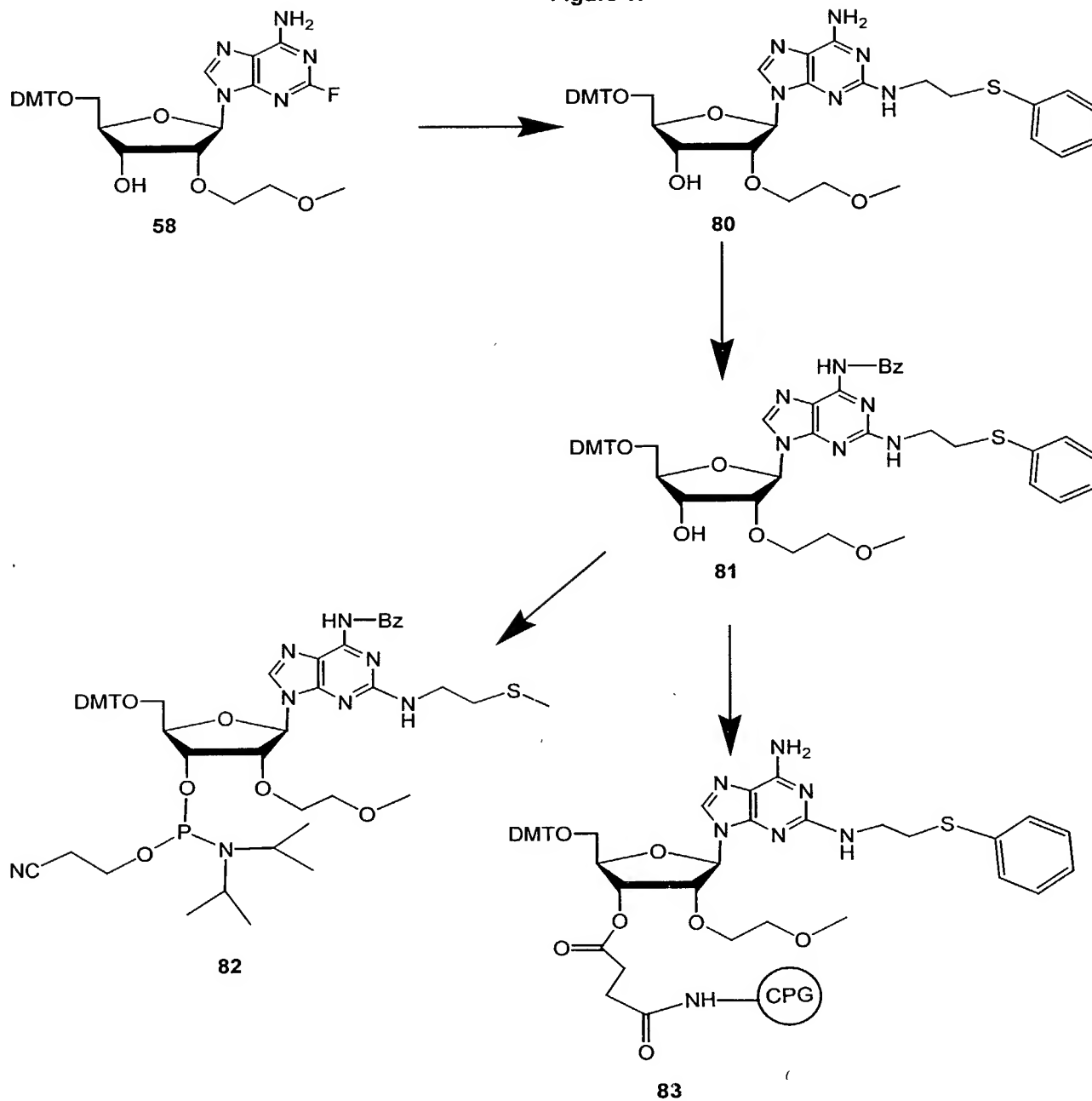




Figure 17

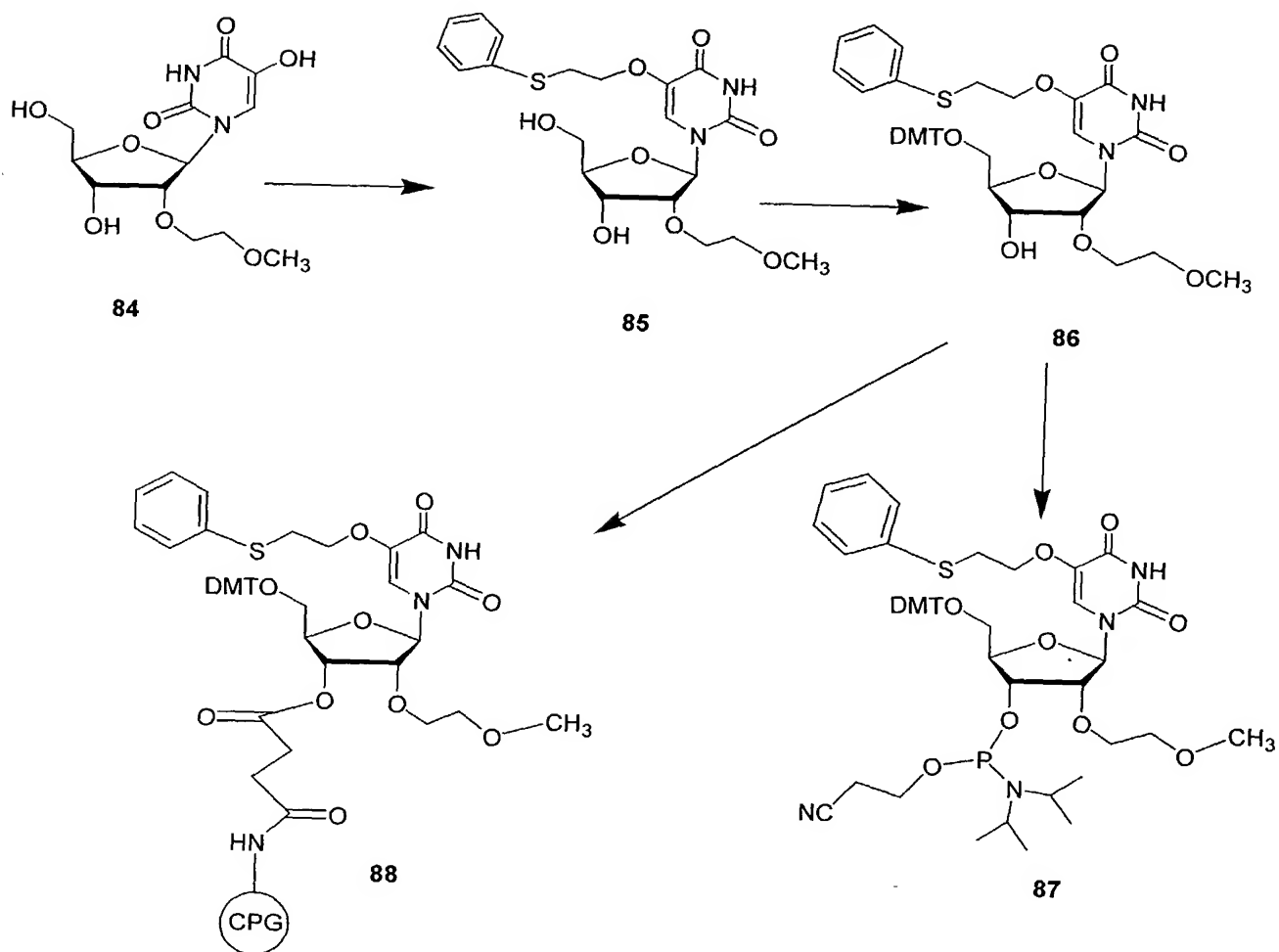


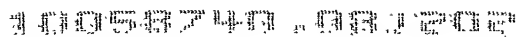


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Figure 18





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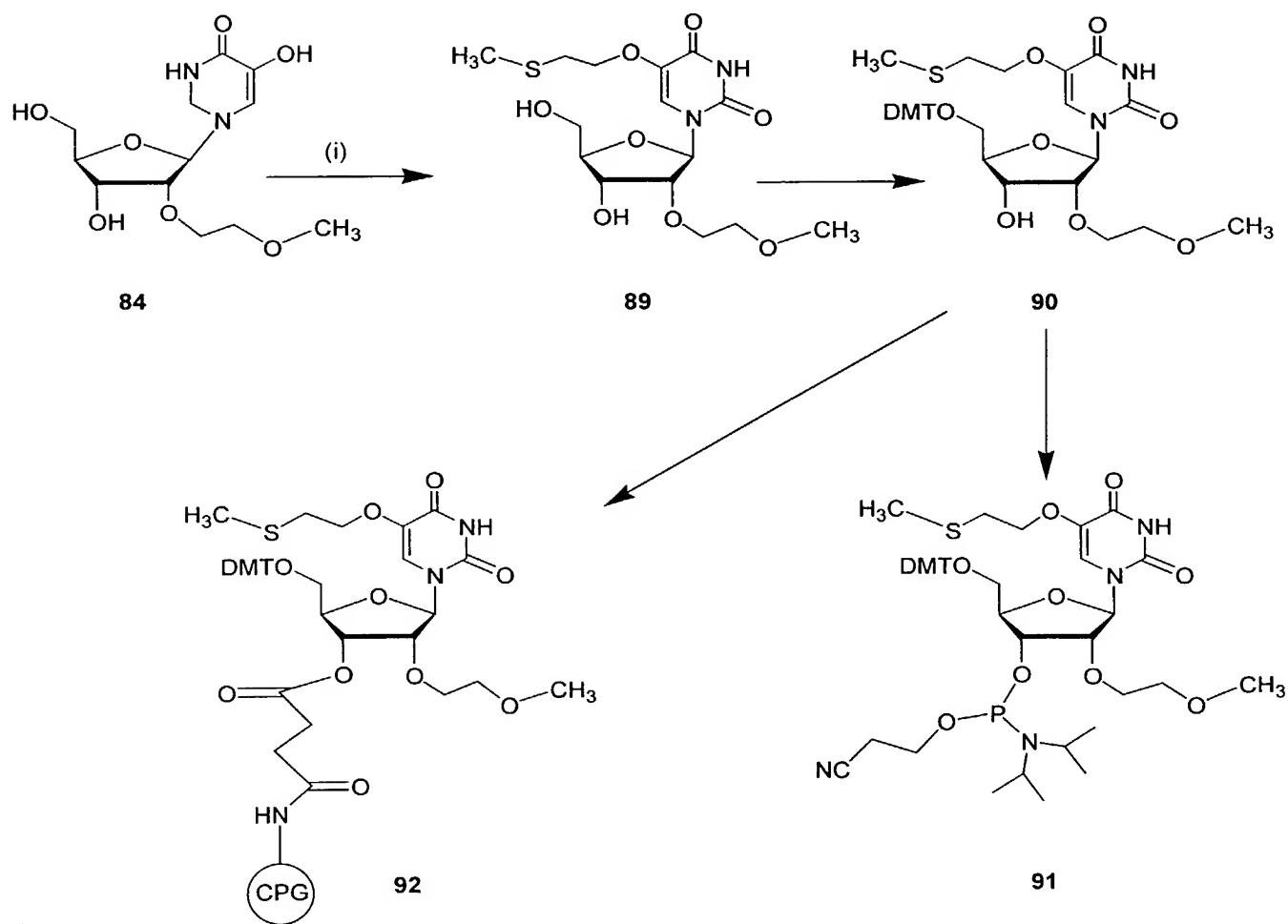
Title. Methods of Modulating Pharmacokinetics of Oligonucleotides

Inventors: Prakash and Manoharan

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The reaction scheme illustrates the synthesis of nucleoside phosphoramidites 91 and 92 from nucleoside 84. Nucleoside 84, which features a 2'-O-methyl group and a 3'-O-methyl group, is converted to nucleoside 89 via reaction (i). Nucleoside 89 is then converted to nucleoside 90, which has a 3'-O-methyl group and a 3'-O-DMTO group. Nucleoside 90 is then converted to nucleoside 91, which has a 3'-O-methyl group and a 3'-O-phosphoramidite group. Nucleoside 91 is then converted to nucleoside 92, which has a 3'-O-methyl group and a 3'-O-phosphoramidite group.





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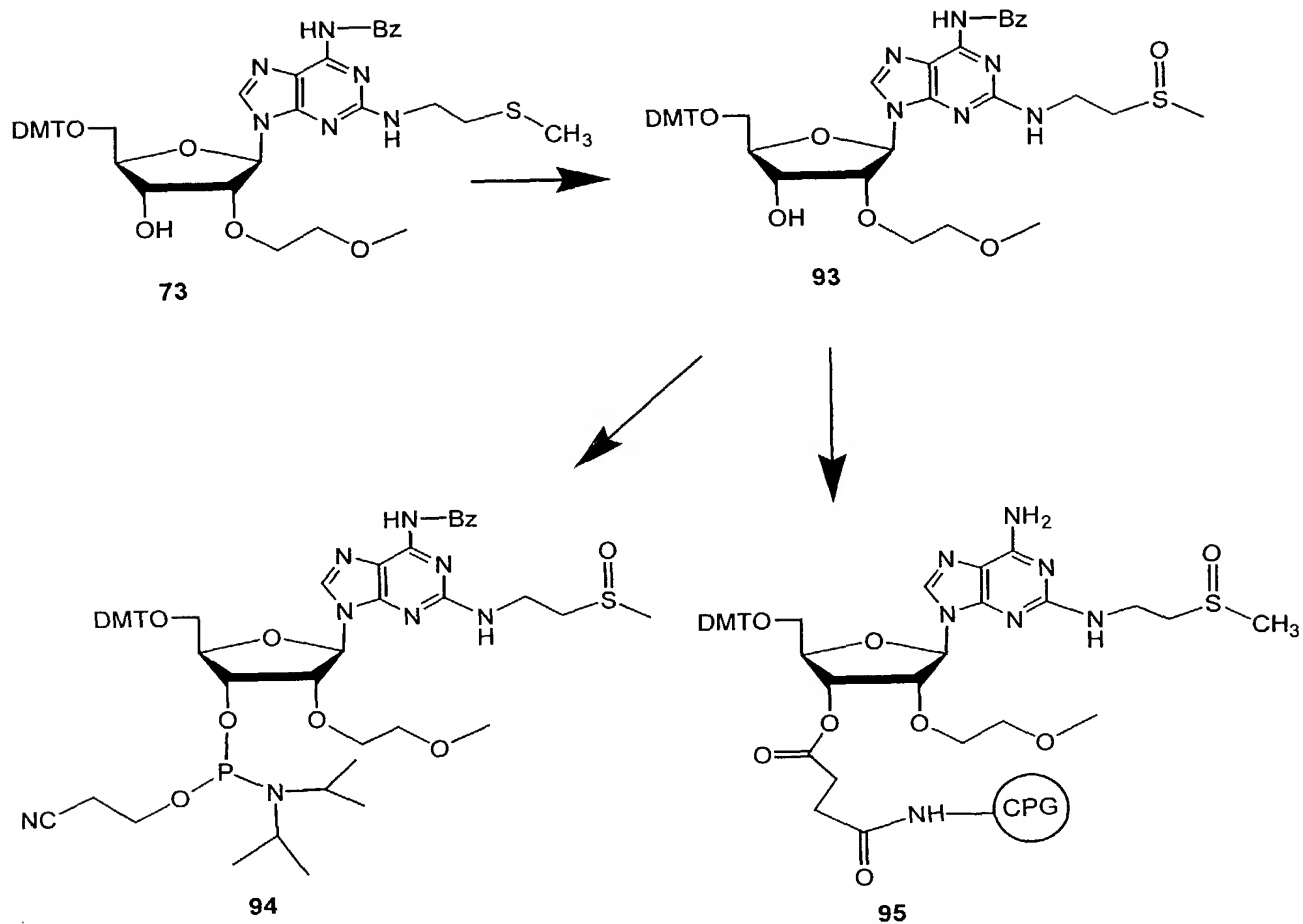
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides

Inventors: Prakash and Manoharan

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Figure 20

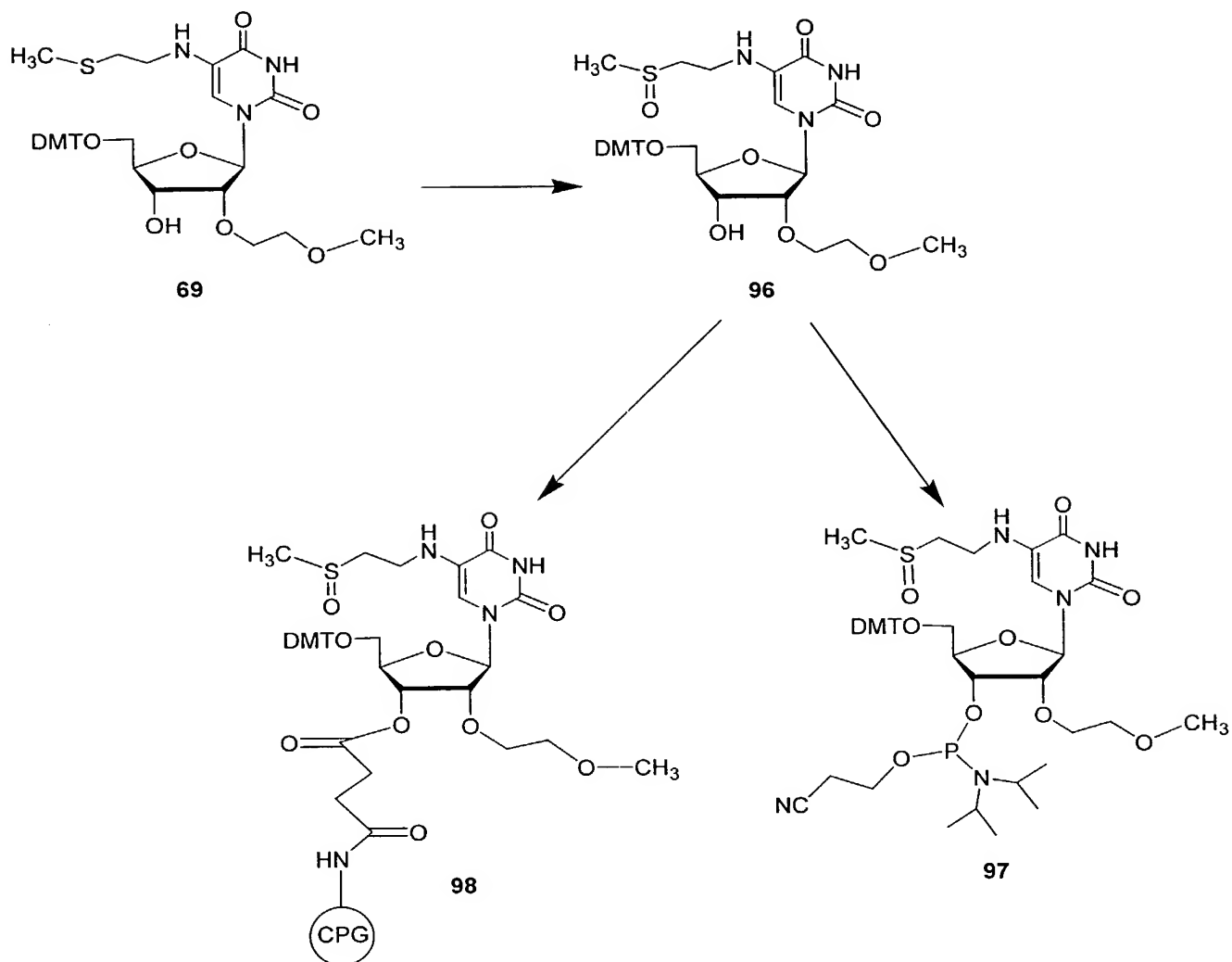




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Figure 21





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Figure 22

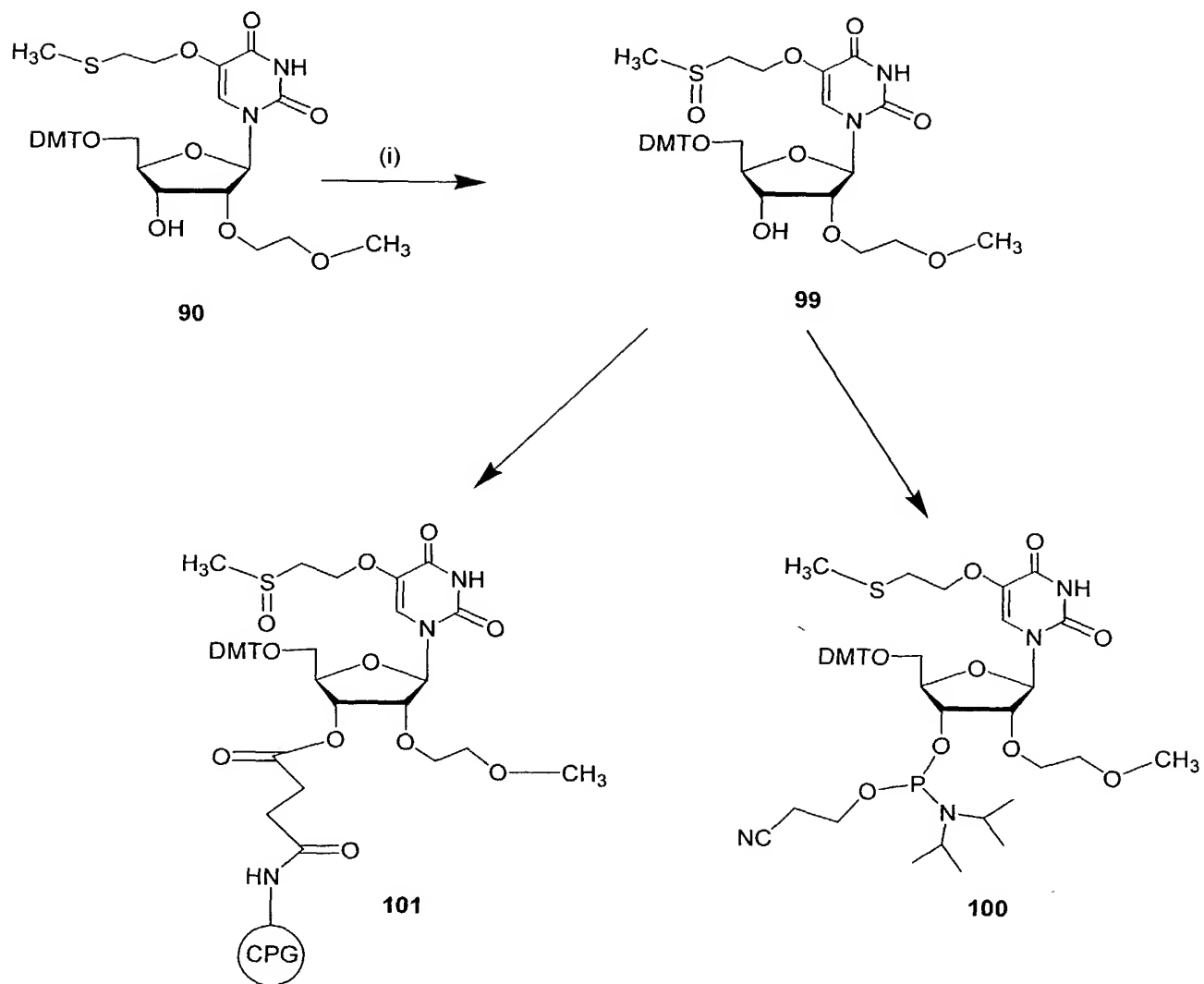
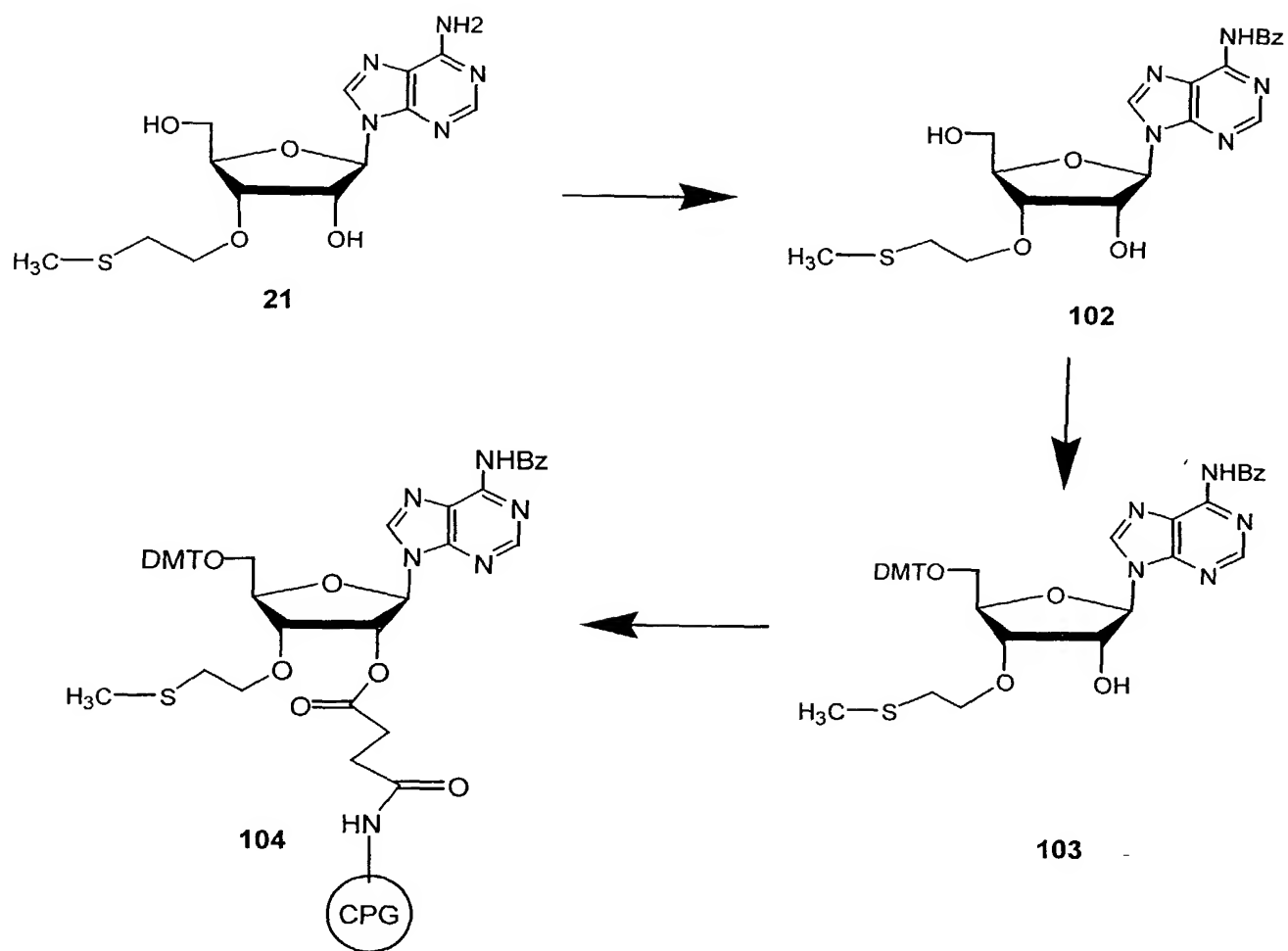




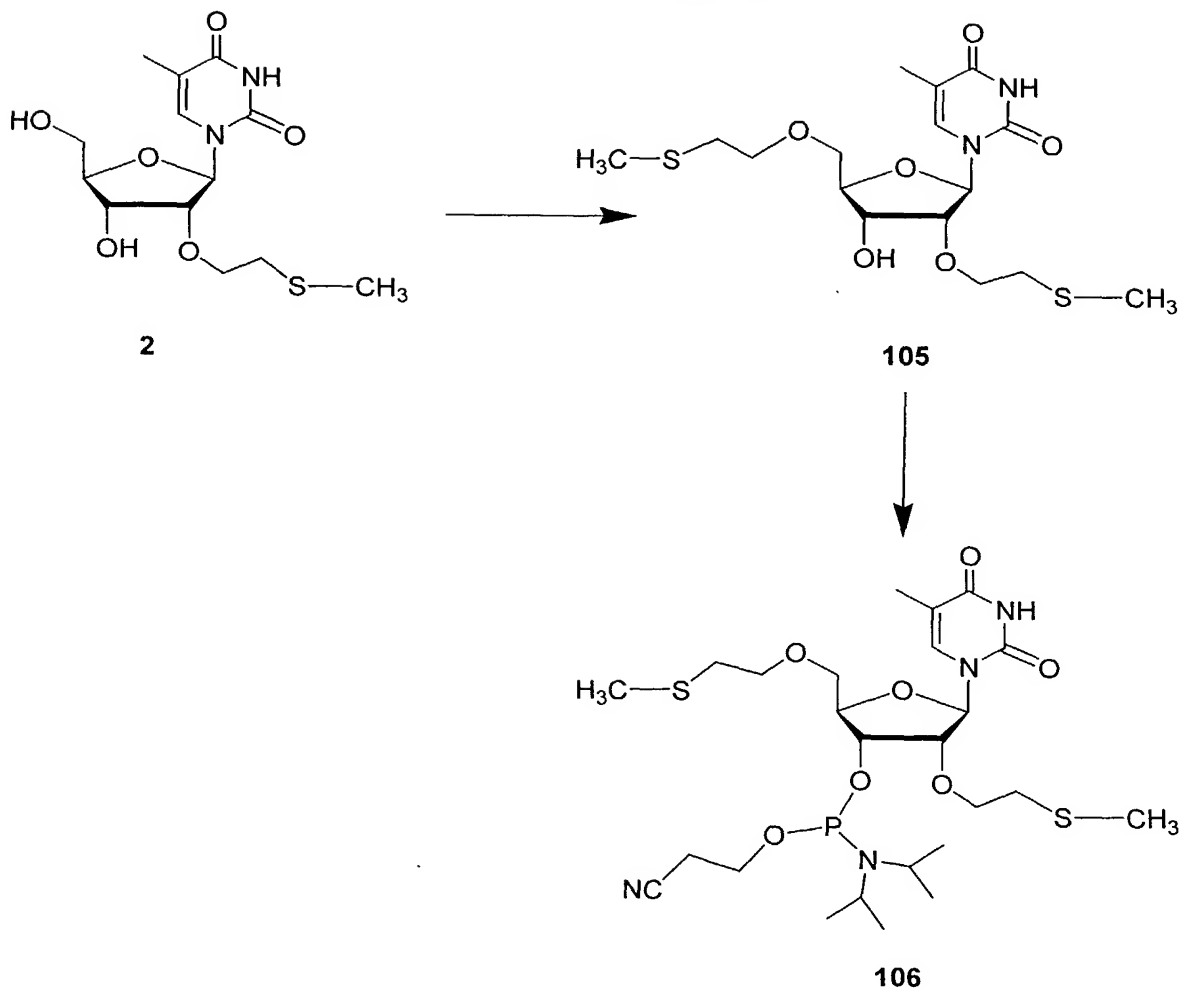
Figure 23





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Figure 24



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Figure 25

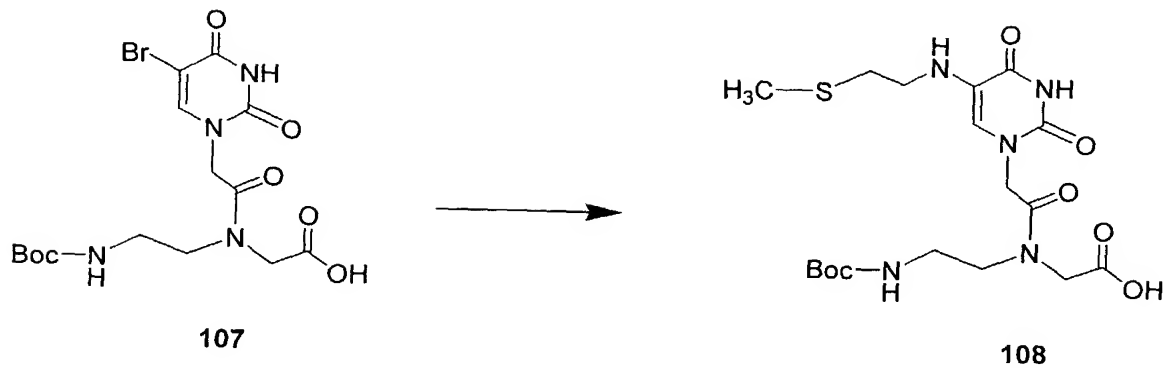
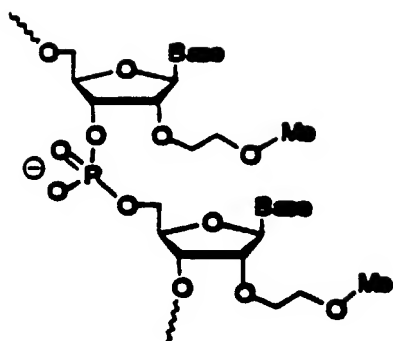




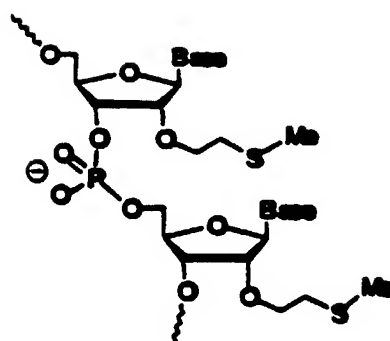
Figure 26



Z-OMDE: Z-O(2-Methoxyethyl)-RNA

$\Delta T_m = 2.0^\circ \text{C}$ (rel. to P=O)

No albumin binding with native
 diester (P=O) backbone



Z-OMTE: Z-O(2-Methylthioethyl)-RNA

$\Delta T_m = 2.0^\circ \text{C}$ (rel. to P=O)

Low-affinity albumin binding with
 native diester (P=O) backbone



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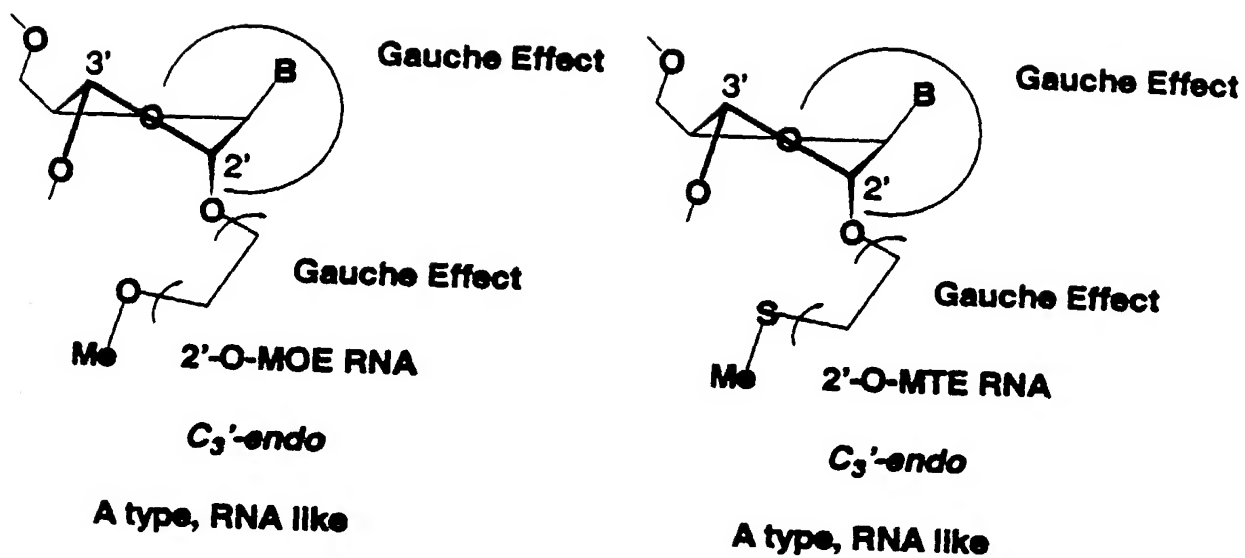
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Figure 27





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Figure 28

